REMARKS

Preliminary Remarks

Claims 107-111 and 117-132 are currently pending and are under examination. Claims 1-88, 89, and 102-106 were previously canceled. Applicants respectfully request entry of the remarks made herein into the file history of the present application.

A. The Rejections of Claims 107-111 and 117-132 Under 35 U.S.C. §§ 103(a) Should Be Withdrawn

Claims 107-111 and 117-132 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Bram *et al.* (WO 98/39361) (hereinafter "Bram PCT") in view of Presta et al. (U.S. Patent No. 5,739,277) (hereinafter "Presta") for "reasons of record."

Claims 107-111 and 117-132 also stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Bram *et al.* (US Patent No. 5,969,102) (hereinafter "Bram US") in view of Presta for "reasons of record."

Applicants respectfully traverse these rejections in view of the following arguments.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, the Examiner must provide a clear articulation of the reasons why the claimed invention would have been obvious, i.e., the Examiner must provide a reason one of ordinary skill in the art would have combined the cited references to arrive at the claimed invention. Second, there must be a reasonable expectation of success. That is, the hypothetical person of ordinary skill in the art, at the time the invention was made, must have had a reasonable expectation that the proposed modification or combination would work to produce beneficial results. *See* MPEP § 2143.02. Finally, "to establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art." *In re Royka*, 490 F.2d 981 (CCPA 1974). The burden of establishing a *prima facie* case of obviousness lies with the Examiner, and the expectation of success must be found in the prior art, not the applicant's disclosure. *In re Dow Chemical*, 5 USPQ 2d 1531 (Fed. Cir. 1988)

i. Bram (PCT and US) Fails to Teach or Suggest the Presently Claimed Fusion Proteins

Bram provides a general disclosure and partial characterization of the TACI protein. Although brief reference is generically made to TACI fragments and TACI fusion proteins, with respect to the TACI extracellular domain only a single fragment consisting of the entire ~ 166 amino acid extracellular domain is specifically disclosed and only a single fusion protein consisting of the ~ 166 amino acid extracellular domain fused to another peptide is disclosed. There is no disclosure of *any* sub-fragment of the TACI extracellular domain (or fusion protein containing same), much less the presently claimed fragments. The presently claimed fragments were simply not taught or suggested by Bram. Therefore Bram cannot provide motivation to the skilled artisan to make fusion proteins containing the specifically claimed fragments. The Examiner appears to argue that because methods for making protein fragments were known, that it would have been obvious to one of ordinary skill in the art to make all possible TACI fragments until, by chance, the presently claimed fragments were produced. In other words, the Examiner bases his finding that claims 107-111 and 117-132 are obvious on an "obvious to try" analysis. As discussed below, such an analysis is not proper in the present case.

a. Relevant Case Law

The U.S. Supreme Court in *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1742 (2007), found that "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of **identified, predictable solutions**, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense." (emphasis added). *Id.* at 1732. Thus, according to the Court, in certain limited situations, a *prima facie* case of obviousness may be predicated on an 'obvious to try' analysis. However, such an analysis is not proper unless: (1) the solutions are identified, small in number and easily traversed in the context of the art and (2) there is a reasonable expectation of success.

The Federal Circuit recently clarified the situations in which an 'obvious to try' analysis may be used to find patent claims obvious. In *Ortho-McNeil Pharmaceutical v. Mylan Labs*, 520 F.3d 1358, 1364 (Fed. Cir. 2008), the Federal Circuit held that patent claims to a pharmaceutical were not obvious in view of the standard set forth in *KSR*. In reaching its decision, the Court

found that, although a key ingredient of the invention may have been one of many a skilled artisan might have tried, evidence showed it was "not the easily traversed, small and finite number of alternatives that KSR suggested might support an inference of obviousness." Moreover, the court referenced the need to avoid "hindsight", stating that the inventor's "pathway to the invention, of course, seems to follow the logical steps to produce these properties, but at the time of invention, the inventor's insights, willingness to confront and overcome obstacles, and yes, even serendipity, cannot be discounted." *Id.* The Court also emphasized that "a flexible TSM test remains the primary guarantor against a non-statutory hindsight analysis such as occurred in this case." *Id.*

In *In re Kubin*, 90 U.S.P.Q.2d 1417, 561 F.3d 1351 (Fed. Cir. 2009), the Federal Circuit set forth factual situations where an obvious to try analysis may not be applied. In particular, "where a defendant merely throws metaphorical darts at a board filled with combinatorial prior art possibilities, courts should not succumb to hindsight claims of obviousness (emphasis added)." *Id* at 1423. According to the Court, such cases are the inverse of the proposition set forth in *KSR* that obviousness may arise where a skilled artisan merely pursues "known options" from a "finite number of identified, predictable solutions," *Id.* In *Kubin*, the prior art disclosed a protein, a monoclonal antibody to the protein, and a routine method by which the DNA encoding the protein could be cloned. The Court found that an obvious to try analysis was proper because practicing the exact method disclosed in the prior art inevitably led to the precise DNA sequence discovered by the inventor. Because this was not a case where the skilled person was faced with combinatorial prior art possibilities, the Court found the obvious to try analysis to be proper and affirmed the lower court's decision that claims covering the encoding DNA were obvious.

b. Analysis

The Examiner acknowledges that Bram PCT and Bram US each fails to disclose (i.e. **identify**) any particular sub-fragment of the TACI extracellular domain, much less sub-fragments consisting of amino acid residues 25-104 or 1-154 of SEQ ID NO: 6. However, according to the Examiner, it would have been obvious to the skilled artisan to produce the specifically claimed fragments of the extracellular domain and test them for observed biological activity. In other words, The Examiner argues that because methods for making protein fragments were known, that it would have been obvious to one of ordinary skill in the art to

make all possible TACI fragments and test them for the ability to bind a then-unidentified ligand until, by chance, the presently claimed fragments were produced.

Such an analysis is contrary to the U.S. Supreme Court and Federal Circuit precedent discussed above. Indeed, the facts of the present case fit squarely within the class of cases for which *Kubin* forbids such an analysis. As discussed in Applicants' prior response, for a polypeptide of a given length, there is an inverse relationship between the number of potential fragments that can be constructed and the size of a given fragment. For a polypeptide of 166 amino acids (corresponding to the TACI extracellular domain disclosed by Bram PCT and Bram US), there are 157 ten-amino acid fragments, 156 eleven-amino acid fragments, 155 twelve-amino acid fragments and so forth. Excluding fragments below 10 amino acids, there are total of (157 + 156 + 155….+ 3 + 2) or 12,402 fragments. Such is not a small or easily traversed number. Even if one were to consider only 80 amino acid fragments (corresponding in size to the claimed fragment consisting of amino acid residues 25-104), there are 87 possible 80-amino acid fragments of the TACI extracellular domain. In any event, the genus of potential fragments is vast and the prior art provides no guidance which could lead the skilled artisan to those specifically claimed. This is not a case where a skilled artisan could merely pursue "known options" from a "finite number of identified, predictable solutions" nor can the vast genus of potential fragments be considered small and/or easily traversed.

Moreover, the skilled artisan would have to test each of the vast number of possible TACI extracellular domain sub-fragments for the ability to bind ztnf4, because Bram PCT and Bram US make only a general statement that the ligand binding domain is located somewhere within the TACI extracellular domain. Neither Bram PCT nor Bram US identify a TACI ligand which could be used to identify which, if any, of the thousands of extracellular fragments retain ligand binding capability. Thus, there is simply no way to predict from Bram PCT or Bram US which if any of the vast number of possible TACI extracellular fragments would constitute ligand-binding fragments.[1] Because Bram (PCT and US) fails to identify any ligand-binding fragment of the TACI extracellular domain or provide any guidance which could lead the skilled

[1] See also Applicants' prior response, in which evidence was filed demonstrating that, at the time of the present invention, it was unpredictable whether protein fragments comprising an extracellular ligand binding domain would retain ligand-binding function.

artisan to the specifically claimed fragments, the skilled artisan would have had to "throw metaphorical darts at a board filled with combinatorial prior art possibilities" in order to arrive at the presently claimed subject matter. Therefore, according to *Kubin*, the Examiner has failed to establish that the claimed subject matter is obvious.

The Examiner, at page 4 of the Office Action, states that *KSR* is the controlling case law with regard to 'obviousness'. However, the Examiner's analysis is improper in view of *KSR*, which limits application of the obvious to try analysis to cases where the prior art discloses a finite number of **identified, predictable solutions**. As discussed above, Bram US and PCT fail to **identify** any TACI extracellular sub-fragment and there is simply no way to **predict** from Bram PCT or Bram US which if any of the vast number of possible TACI extracellular fragments would constitute ligand-binding fragments.

The Examiner also attempts to distinguish the fact pattern in *Ortho-McNeil* from the present case. However, Applicants cited *Ortho-McNeil* for the guidance provided by Federal Circuit to those applying the principles set forth in *KSR*, which guidance is not limited to the fact pattern of that case. As acknowledged by the Examiner, the Federal Circuit in *Ortho-McNeil* warned that the "obvious to try" analysis discussed in *KSR* is only properly applied in situations with a finite and in the context of the art, small and/or easily traversed number of options. If it is the Examiner's contention that court decisions are only applicable to cases with identical fact patterns, then *KSR* would seem to be inapposite to the present case as well, as it dealt with gas pedal technology and not fusion proteins for medical use. At any rate, as discussed above, the number of possible TACI extracellular domain is over **12,000**, which one of ordinary skill in the art would not consider to be a small **or** easily traversed number as alleged by the Examiner, particularly in view of the fact that TACI ligands were unknown at the priority date of the present application.

The disclosure of Presta does nothing to rectify the aforementioned failure of Bram PCT and Bram US to disclose the specifically claimed fragments.

Based on the aforementioned, it is clear that the Examiner has improperly applied an "obvious to try" standard in finding the claims obvious over the cited prior art. Here, the prior art teaches generally that the ligand binding portion of TACI is located somewhere on the extracellular domain. The Examiner's contention that it would have been obvious to make and

screen the multitude of fragments representing all possible overlapping peptides derived from the protein in order to find the specifically claimed ligand binding fragment is directly analogous to throwing "metaphorical darts at a board filled with combinatorial prior art possibilities" which, according to the Federal Circuit's decision in *Kubin* cannot serve as the basis for finding claims 107-111 and 117-132 obvious. In this respect, it is clear that the Examiner has impermissibly used hindsight reconstruction to retrace the path of the present inventors and discounted the number of possible TACI extracellular domain sub-fragments. Thus, the pending claims are, as a matter of law, nonobvious over each of Bram PCT and Bram US in view Presta under 35 U.S.C. § 103(a) and the Applicants respectfully request withdrawal of the rejections.

ii. Bram (PCT and US) Fails to Provide a Reasonable Expectation of Success

Applicants also respectfully submit that Bram PCT and Bram US each fails to provide a reasonable expectation of success in achieving the presently claimed methods. Whether the prior art provides a reasonable expectation of success is made at the time the invention was made. *Ex parte Erlich*, 3 USPQ2d 1011 (Bd. Pat. App. & Inter. 1986). Moreover, to "to have a reasonable expectation of success, one must be motivated to do more than merely to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 165 (Fed. Cir. 2006). Finally, a reasonable expectation of success requires more than where the prior art teaches merely to pursue a "general approach that seemed to be a promising field of experimentation" or "gave only general guidance as to the particular from of the claimed invention or how to achieve it." *Medichem*, 437 F.3d at 1167.

The biotechnological arts are inherently unpredictable. This is particularly the case where, as here, recombinant proteins are administered to achieve a therapeutic effect. Indeed, there is inherently a tremendous amount of uncertainty as to the *in vivo* effects when administering a recombinant protein into a mammal. Bram PCT and Bram US each fails to provide any guidance that could lead one of ordinary skill in the art to expect that administration of the claimed fusion proteins would be effective in inhibiting B lymphocyte proliferation.

It is undisputed that Bram PCT and Bram US each fails to disclose *any* ligand that binds the TACI receptor. In the absence of any known TACI ligand, one of ordinary skill in the art

had no reliable screening method for determining whether a fusion protein containing a sub-fragment of the TACI extracellular domain would retain the ability to bind ztnf4. No guidance is provided by Bram PCT or Bram US as to particular sub-fragments that would be likely to retain this ability, nor has the Examiner pointed to any such guidance in either reference. Without a ligand with which to screen such fusion proteins *in vitro*, one of ordinary skill in the art is left to create fragments of the TACI extracellular domain without guidance as to which portion of the TACI extracellular domain is required for interaction with ztnf4, fuse these fragments to an immunoglobulin constant domain, administer the fusion proteins to a mammal and hope that the mammal manifests a reduction in B lymphocyte proliferation. Importantly, Bram (PCT and US) does not provide any working example demonstrating efficacy *in vivo* of any fusion protein containing any TACI fragment. Only through the present disclosure is one of ordinary skill taught the identity of ztnf4 as a ligand for the TACI receptor. Applicants respectfully submit that the Examiner's conclusion of obviousness amounts to impermissible hindsight reconstruction based on information gleaned from the present disclosure.

Presta, while teaching the fusion of the Fc fragment with other proteins to increase the circulating half-life, fails to remedy the aforementioned infirmities of Bram PCT and Bram US.

As discussed above, Bram PCT and Bram US each provides only a general approach to a promising field of experimentation and provides nothing more than general guidance as to how to achieve the presently claimed invention. Accordingly, for at least this reason, Bram PCT and Bram US each fails to render the subject matter of the present claims obvious. Withdrawal of the rejections of claims 107-111 and 117-132 under 35 U.S.C. § 103(a) is thus requested.

B. <u>The Rejections for Obviousness-type Double Patenting</u>

Claims 107-109, 117-119 and 122-123 stand rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-4 of copending Application No. 11/748,978. Claims 107-109 and 117-119 are newly rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 84-86 of copending Application No. 09/569,245. Applicants wish to defer the response to these provisional rejections until the claims are otherwise allowable.

Conclusion

In view of the above remarks, applicants respectfully submit that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the instant application, the Examiner is encouraged to call the undersigned at (312) 595-1408. Should any additional fees be deemed necessary in connection with the filing of this document, the Commissioner is hereby authorized to deduct any such fees from Deposit Account No. 08-3038 referencing the above attorney docket number.

Respectfully submitted,

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